Journal of
Clinical & Medical Images
Case Reports

Open Access | Review Article

# Advances in the treatment of diabetic peripheral neuropathy

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## Abstract

Diabetic peripheral neuropathy is a common complication of diabetes mellitus, and the number of patients is increasing year by year, which greatly affects the quality of life of patients. However, the pathogenesis of diabetic peripheral neuropathy has not been adequately researched yet, and clinically there is a lack of effective therapeutic measures to reverse the disease. Aiming at the possible pathogenesis of diabetic peripheral neuropathy and the current application of rehabilitation therapy, Chinese medicine physiotherapy and pain medicine in the field of diabetic peripheral neuropathy, this paper summarized, in order to provide help for the treatment of diabetic peripheral neuropathy.

**Received:** Feb 29, 2024

**Accepted:** Mar 18, 2024

**Published Online:** Mar 25, 2024



**Keywords:** Diabetic Peripheral Neuropathy; Oxidative Stress; Low Energy Laser Treatment; Traditional Chinese Medicine Fumigation; Pulse Radiation Frequency.

**Cite this article:** Shu C; Zhang YF; Zhang W; Rao Y; Li X; et.al.,. Advances in the treatment of diabetic peripheral neuropathy. J Clin Med Images Case Rep. 2024; 4(1): 1655.

## Introduction

Diabetes mellitus is a public health problem, with nearly half a billion people worldwide suffering from diabetes, and the prevalence of diabetes is increasing year by year, affecting about 578 million people by 2030 and about 700 million people by 2045 [1]. Diabetic peripheral neuropathy (DPN) is the focus of this paper. DPN usually presents with sensory symptoms, including numbness and pain, and has a great impact on the quality of life of patients. The pathogenesis of DPN was still not fully understood [2], and commonly used therapeutic medications in clinical practice include nutrient neurotropic drugs, tricyclic antidepressants, anticonvulsants, narcotic and non-narcotic analgesics, which could only alleviate symptoms or delay the progression of DPN, and lack of effective therapies that could stop or reverse the process of DPN [3], urgently need drug research from the pathogenesis. The currently discovered pathogenic mechanisms of DPN included metabolic disorders, oxidative stress, impaired cellular autophilia, nerve injury, neuroinflammation, and neurotrophic factor deficiency. This article discussed the latest drug therapy progress from the above mechanisms. In recent years, multidisciplinary cross-treatment has also been a hot trend, and rehabilitation therapy, Chinese physiotherapy and pain medicine have also been utilized in the treatment of DNP.

## Pathogenesis and drug therapy

**Metabolic disorders and treatment**: Abnormal blood sugar and blood lipid were easy to lead to DPN. Appropriate weight loss in obese patients with high blood lipids was an important part of clinical education. Scientific weight loss was associated with improvement in all metabolic parameters except blood pressure [4]. Exercise significantly improved nerve velocity conduction, peripheral sensory function, and peak foot pressure distribution in the lower extremities while controlling weight, and was an effective non-pharmacological intervention to improve diabetic foot-related outcomes. Scientific weight loss through moderate exercise reduced blood lipids and controls metabolic disorders [5]. Reasonable exercise and scientific weight reduction should be advocated for DPN patients with dysglycemia and dyslipidemia in clinical work.

**Oxidative stress and treatment**: Under hyperglycemic conditions, excess pyruvate produced by glycolysis might damage neurons and lead to oxidative stress [6]. Oxidative stress damaged mitochondria and other neuronal cellular components, Schwann cells, and microvascular endothelial cells, accelerating neuropathy. Inhibition of oxidative stress directly reduced nerve damage and improved nerve conduction. Hedysarum polysaccharide (HPS) is the active component of Hedysarum, a plant widely used as food and herbal medicine for the treatment of many diseases. Liu He et al. [7] tube-fed a mouse model of DPN for 8 weeks with either 50, 100, and

200 mg/kg/d of HPS or 30 mg/kg/d of lipoic acid (control group) showed that HPS significantly increased motor nerve conduction velocity, shortened heat withdrawal latency, and inhibited oxidative stress in serum and sciatic nerve in a mouse model of DPN. The mechanism of HPS was to regulate oxidative stress by activating the Keap1/Nrf2 signaling pathway, which results in a protective effect against DPN.

**Cellular autophagy disorders and therapy**: Autophagy was an ancient process of self-degradation in all eukaryotic cells as a means to fulfill the metabolic needs of the cell itself and the renewal of its organelles, and had a role in regulating cell proliferation, differentiation, senescence and apoptosis [8]. In DPN, autophagy had been found to be inhibited in Schwann cells [9]. Matrix metalloproteinase 9 (MMP9) belongs to the MMP family, and intracellular MMP9 had also been revealed to regulate cell death, autophagy and epigenetic modifications [10]. Adenylate-activated protein kinase (AMPK) restored metabolic homeostasis during metabolic stress. The AMPK pathway was involved in the pathogenesis of tumors, inflammation, obesity and diabetes [11,12]. Lycorine is an alkaloid isolated from species of the alfalfa family and has a variety of biological activities, such as antitumor, antiviral and anti-inflammatory [13]. Qingqing Yuan et al. [14] found that Lycorine is a possible agent for reversing the gene differentiation in diabetic peripheral neuropathy through data analysis. In vitro experiments verified that in high glucose-treated rat, Lycorine treatment activated the metabolic pathway AMPK, as well as decreased the expression of MMP9 in diabetic Schwann cells, which in turn promoted autophagy in Schwann cells. High glucose up-regulated MMP9 expression by 1.37-fold in rat Schwann cells. After being exposed to lycorine, the expression of the MMP9 protein dropped by 51.59%. Lycorine is a promising agent for diabetic peripheral neuropathy by promoting cellular autophagy and treating Schwann cell dysfunction.

**Nerve damage and treatment**: The pathology of DPN was characterized by diffuse damage to peripheral nerve fibers. JuanZhen Yang et al. [15] built a platform to screen the natural products in the laboratory, searching for active compounds that could prevent the growth damage of dorsal calcaneus ganglia of diabetic mice, and obtained Magnolol (MG), a natural product extracted from mango. Peroxisome proliferator-activated receptor γ (PPARγ) was considered a promising therapeutic target for many diseases, and PPARγ expression was down-regulated in peroneal nerve tissues of patients with progressive DPN[16] .Many results suggested the significance of PPARγ regulation in DPN pathology. A deep study of the dorsal heel ganglion and sciatic nerve in diabetic mice with PPARγ-specific knockdown demonstrated that MG enhanced nerve axon growth in the dorsal root ganglion, increased intraepidermal nerve fiber density and protected the myelin structure in DPN mice via PPARγ. MG as an agonist of PPARγ effectively ameliorated the DPN-like pathological changes in the mice, demonstrating the potential of MG in the treatment of DPN.

**Neuroinflammation and treatment**: Neurogenic inflammation had been implicated in the pathogenesis of DPN[17,18], and the release of inflammatory factors was inextricably linked to abnormal nerve excitation and the development of pain. Studies had shown that inflammatory factors such as tumor necrosis factor (TNF) and interleukin (IL) were increased in DPN [19]. Inflammatory factors triggered an inflammatory cascade that impaired the function and structure of peripheral nerves, including myelin damage and microangiopathy. Cytokines such as TNF, IL-1 and IL-6 promoted sensitization of the peripheral nervous system to produce neuropathic pain. Bing jia Zhao et al. [20] found that quercetin down-regulated key proteins of TLR4, MyD88, and NF-κB in the TLR4/MyD88/NF-κB pathway, which in turn reduced the inflammatory factors such as TNF-α, IL-1 β and IL-6 levels in DPN rats, exerting neuroprotective and anti-inflammatory effects to improve the deterioration of neurological function. Therefore quercetin is a potential candidate for the treatment of DPN.

**Neurotrophic factor deficiency and treatment**: Fitional neurological measures for patients with DPN. Vitamin B12 is an adjunctive or integrative therapeutic agent for pain conditions [21], and Uroš Pecikoza [22] found that metformin synergized with vitamin B12 to reduce mechanical nociceptive hypersensitivity in diabetic animals. Metformin-induced vitamin B12 deficiency had been associated with worsening diabetic neuropathy, and the combined use of metformin and vitamin B12 circumvented this potential adverse effect. J. Jesisca [23] conducted a prospective case series study designed for 43 patients with DPN who were given oral vitamin tablets (vitamin B1 100 mg, vitamin B6 100 mg, vitamin B12 5000 mcg), once a day for 1 month. Pain scores were performed using visual analog scale at the initial visit, day 14 and day 30. The results showed that combined treatment with vitamins B1, B6, and B12 significantly reduced pain intensity in patients with diabetic peripheral neuropathy.

Vitamin D deficiency was common among diabetics. Several studies had reported that vitamin D intake might prevent or delay the onset of diabetes and reduced associated complications. Vitamin D deficiency was associated with low neurotrophic factor, which was necessary for the proper functioning of neurons. Vitamin D was involved in the synthesis of neurotransmitter-related enzymes and brain detoxifying substances. Vitamin D was a potent neurotrophin and inducer of neurotransmitters. Akram Ghadiri-Anari et al. [24] showed that supplementation of vitamin D improved the signs and symptoms of DPN. Kaissar Yammine et al. [25] found that achieving absolute serum levels of vitamin D significantly reduced pain level in patients with DPN. All of the above studies suggested the efficacy of vitamin D in the treatment of DPN.

**Ion channel and treatment**: Ca2+ channels play a key role in the control of sensory functions associated with the transmission, processing and modulation of pain signals, for example gabapentin analogs such as gabapentin and pregabalin exert analgesic effects by binding to the α2δ-1 and α2δ-2 Ca2+ channel subunits [26]. Studies had shown that gabapentin and pregabalin had significant efficacy in the treatment of DPN [27]. Calcium channel blockers are effective analgesic drugs and also have significant efficacy in the treatment of DPN.

## Physical factor therapy

**Low-level laser therapy**: Low-level laser therapy (LLLT) has the function of regulating endocrine, anti-inflammatory and analgesic, regulating nerves and immune function. LLLT uses low-intensity light to produce photochemical effects, leading to some biochemical changes in cells. The power range of LLLT is from 10mW to 500mW, and the wavelength is from 660 to 905nm. LLLT has the potential to produce biostimulating effects on the nervous system and therefore holds promise for the treatment of nerve damage. Anju M. et al [28] studied 40 patients with diabetic neuropathy ranging in age from 30 to 70 years and all subjects included in the study were treated with

two low energy lasers. EC laser (wavelength 632.8nm, dose 3.1J/cm2) and Thor laser (wavelength 660nm and 850nm, dose 3.4J/cm2) were used to irradiate the plantar and dorsal foot. Four weeks after both laser interventions all participants had decreased Michigan Neuropathy Screening Scale scores and Digital Pain Rating Scale scores, significantly improved vibration perception, and elevated serum vitamin D and magnesium compared to pre-treatment. The result suggested that LLLT significantly relieved pain and sensory perception in patients with DPN.

**Low-frequency pulsed ultrasound therapy**: Bilir-Yildiz et al [29] performed low frequency pulsed ultrasound therapy on cisplatin-induced chemical neuropathy in rats using ultrasound therapeutic instrument. Ultrasound was applied to the skin area approximately 5cm2 above the sciatic nerve on the lateral thigh of the hind limb of rats for 3 minutes, which revealed that low-frequency pulsed ultrasound treatment improved neurological dysfunction in cisplatin-induced peripheral neuropathy by decreasing oxidative stress and inflammation, modulating apoptosis and mitochondrial autophagy, and decreasing demyelination and neurodegeneration, resulting in improved motor nerve conduction and sensation of injurious pain. Therefore, low-frequency pulsed ultrasound therapy is a potential strategy for the treatment of chemotherapy-induced neuropathy and deserves further study.

## Chinese medicine physiotherapy

**Chinese medicine fumigation**: In recent years, Chinese medicine has played an important role in the prevention and treatment of chronic diseases in the world. Fumigation therapy can directly act on the affected area of the patient, and the heat generated when the drug boiling promotes blood circulation, accelerates human metabolism, and allows the active ingredients of the drug to penetrate into the skin through the heat. Different formulas can be used with different efficacy. Single-flavored Chinese medicines commonly used in clinical practice include astragalus, angelica sinensis, rhizome of Chuanxiong, laurus nobilis and cauliflower, etc. Different compound formulas can also be selected according to the identification of Chinese medicine evidence. Compared with Western medicines, Chinese herbs are mild in efficacy and less toxic. Studies had shown that herbal fumigation could improve the symptoms of DPN and increase nerve conduction velocity [30].

**Gua Sha**: Gua sha therapy involves pressing specific areas of the body with a smooth-edged instrument that produces transient red or purple petechiae and ecchymoses, which usually subside within a few days, and can be defined as instrument-assisted mechanical stimulation of the body surface. Gua sha treatment is usually well tolerated with little discomfort. According to preclinical studies, gua sha had anti-inflammatory and immunoprotective effects by increasing microperfusion and up-regulating heme oxygenase [31]. Xiaolan Xie et al. [32] conducted a study using gua sha therapy to treat diabetic peripheral neuropathy showing that gua sha therapy significantly reduced the severity of neuropathy symptoms, improved sensory function, reduced peripheral arterial disease, and better control of blood glucose levels thereby improving the quality of life compared to the control group.

## Pain Medicine

**Pulsed Radiofrequency**: Pulsed Radiofrequency (PRF) therapy is a kind of neuromodulation therapy that uses special equipment and puncture needles to precisely output ultra-high frequency radio waves to act on specific areas. It improves the ATP metabolism of sensory nerve fibers and the function of partially inactivated ion channels, thus effectively inhibiting the excitatory afferents of pain fibers and relieving pain without destroying the structure of nerve fibers. PRF has been widely used for the treatment of a variety of neuropathic pain, including herpes zoster-related pain, lumbar disc herniation, and frozen shoulder. Abd-Elsayed et al. [33] conducted a retrospective study to collect a series of peripheral neuralgia patients who received PRF, confirming the potential of PRF in treating peripheral neuralgia that failed to respond to conservative treatment.

**High-frequency spinal cord electrical stimulation**: Painful diabetic peripheral neuropathy (pDPN) is a key factor affecting quality of life. Among Chinese DPN patients, the prevalence of pDPN is as high as 57.2% [34]. pDPN patients are more likely to suffer from depression, anxiety, sleep disorders and foot amputation [35]. In terms of non-pharmacological interventions, neuromodulation of pain is an alternative approach worth exploring. A randomized controlled trial showed that 10 kHz electrical nerve stimulation could safely and effectively treat patients with refractory pPDN, relieving pain and improving quality of life [36]. There was a risk of infection with electrical spinal cord stimulation, but fatal complications were rare. Comprehensive patient assessment before spinal cord stimulation implantation and multidisciplinary collaboration after implantation were recommended so as to minimize complications and further improved treatment outcomes [37]. High-frequency spinal cord electrical stimulation is a permitted new therapeutic modality and is a viable treatment modality to provide pain relief for the pDPN [38].

## Summary

The prevalence of diabetes is increasing every year, and DPN is a common complication of diabetes, for which there is a lack of effective methods to treat the disease. DPN could occur despite good glycemic control. We expect to have a deeper understanding of the pathogenesis of DPN and find more effective treatments. Based on the possible pathogenesis of DPN, this paper seeked drugs to reverse the disease or delay its progression. Low-energy laser and low-frequency pulse ultrasound therapy were widely used in fracture, lumbar and cervical pain, which also had certain effects on relieving pain and numbness and improving nerve conduction speed in DPN patients. Physical factor therapy has a promising future in diabetes and its complications with the development of rehabilitation medicine. Chinese medicine physiotherapy had rich experience in the treatment of diabetes and its complications, and had various therapeutic methods, which was a very promising treatment method. Pain in pDPN patients seriously affected the quality of daily life, and pain relief was the first priority. In recent years, many non-drug treatment methods of pain medicine had been gradually applied to pDPN patients, which were safer, more convenient and effective than conventional drug treatment. Drugs, rehabilitation therapy, Chinese medicine physiotherapy, and pain medicine are effective methods for the treatment of DPN, and we hope this paper can provide various ideas for the clinical treatment of DPN patients.

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